RESEARCH ON TOBACCO AND HEALTH

(The first half dozen pages will restate much of the material contained in the first six pages of my previous statement to the Senate Committee)

We understand that the present Congress is receiving requests for very large appropriations to finance research relating to tobacco use and human health. In the public interest, it is certainly important that such funds should be utilized for studies of the kinds most likely to provide practical results in terms of improved public health and diminution in the toll of those diseases that are currently the greatest causes of illness and premature death.

Since The Council for Tobacco Research has been engaged for thirteen years in its efforts to find and pursue the most effective approaches to these very problems, I am undertaking, as a public duty, to point out some of the avenues that I believe should be explored with all the resources and talent that can be brought to bear.

Within the last century very notable progress has been made in the conquest of the infectious diseases with a consequent great rise in life expectation. This medical triumph has produced a population containing a larger proportion of older persons than any heretofore encountered in history. With this increase in the older population, disability and death due to constitutional ailments such as cancer, disorders of the heart and arteries, and chronic respiratory diseases have shown a relative increase, just as rocks appear to rise from the water as the tides recede. Further progress in improving life expectancy must therefore come largely from new methods of deferring the development of such constitutional diseases, which characteristically are likely to have a slow and insidious onset.

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The many astute medical advisers whom we have consulted during these thirteen years have been unanimous in pointing out the complexities that are to be expected in the etiology or causation of such diseases. Their origin and development involve various degrees of host susceptibility or of resistance which are deep-seated in the constitutional genetic nature of each human individual. Susceptibility or resistance may also be affected importantly during the life span by such factors as age, sex, degree of activity of various glands of internal secretion and the numerous enzyme systems of the body, as well as by the nature of the diet and the individual characteristics of food absorption, utilization, storage and excretion. Habits of daily life such as exercise, hours of sleep, use of coffee, tea, alcohol and the common household drugs, exposure to noxious agents in the job, psychological characteristics and the stresses that assail the psycho-physiological systems, undoubtedly play a role, as do also the numerous bacterial and virus infections, mild or acute, which all persons still experience even though these are much less often fatal than formerly.

It is just such constitutional diseases which epidemiological studies a few years ago reported to be more frequent among cigarette smokers than among non-smokers. The list of diseases so associated extends to a score or more.

While these reports have been and still are the subject of debate among statisticians as to their reliability on technical grounds, I do not feel competent to discuss this phase of the question and shall not consider it here at any length.

It is perfectly evident, however, even to the non-expert, that the reliability of any association of any disease with any other factor will depend very greatly upon the reliability with which the disease can be detected, distinguished from other conditions with similar characteristics, and recorded under a name that is generally understood, accepted and agreed upon. The true

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incidence of many diseases and rates of mortality from the same are greatly clouded by variable and rapidly changing diagnostic acumen, problems of definition and differentiation, and variations in nomenclature. Time trends in incidence are much more clouded by such variations than current figures. Only the figures for total mortality from all diseases escape the complication of variations in diagnosis, definition and nomenclature. However, since epidemiologists have also reported a higher total mortality among cigarette smokers than among non-smokers, this statistical association also will be considered further.

It is a fact of history that these epidemiological reports provided the impetus for the abundant research relating in one way or another to tobacco and health that has subsequently been undertaken by many scientists and has been sponsored not only by Government departments but by a number of voluntary health associations and foundations. including AMA & CTR.

Because of the baffling nature of the constitutional diseases and their relative increase as causes of disability and death, it is natural that any new observation that seemed to point toward a method of even partial control should arouse excitement and demands for quick action. Unfortunately action based on it prematurely on an incomplete scientific basis can be extremely costly and disillusioning.

While any thought of tobacco prohibition is disclaimed in practically all quarters, an "abolition psychology" has nevertheless evolved which many feel is unpromising of substantial effect with respect to the recognized goals of constitutional disease control. The probability that large numbers of persons will continue smoking imposes the necessity of defining the hazards, if there be hazards, and of pursuing research that may remove or reduce them. As of this moment, these reputed hazards are still (almost wholly) unidentified on any firm scientific basis.

What are the defined hazards

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It must be remembered that all the constitutional diseases mentioned above as statistically associated with cigarette smoking occurred and most were well-known when the use of cigarettes was very uncommon. They still occur among non-smokers. Hence any real or hypothetical effect of smoking on health can be, at most, no more than a contributory or aggravating factor rather than an "all or nothing" cause of any of these conditions.

Since the beginning of our research program this Council has sought the advice of many able and well-recognized statisticians with respect to the implications of the associations cited. These have been unanimous in pointing out and emphasizing that the mathematical association of one variable with another does not establish that one is the "cause" of the other. A positive association is consistent with the possibility of a causal relationship but causation cannot be considered established until all (reasonable) ? alternative) possibilities have been ruled out. This is no easy matter.

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A reported association between the incidence of any particular disease and cigarette smoking therefore asks more questions than it answers. Some of these questions may be stated as follows:

1. Is cigarette smoking actually a "causal factor" in the disease? That is, does it contribute in some way to its etiology, whether weakly, strongly, directly or indirectly?
2. Is cigarette smoking rather instead a sign or indicator of the presence of some congenital ? characteristic that predisposes to the disease?
3. Is cigarette smoking a practice that happens to accompany some pattern of living habits or practices that cause, predispose to or aggravate the disease, without itself being involved causally?

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4. Is the association fortuitous or a technical artifact due for example, to changing trends in ability to recognize the disease, to distinguish it from others and to record it under a definitive name?

A more simple and common-sense manner of stating these questions may be put as follows: Do people really develop this disease because they smoke cigarettes or is it rather that the kinds of people most likely to develop the disease on account of their hereditary nature or particular patterns of life and behavior have an increased need or desire to smoke cigarettes?

The answer may not be the same for all the score of diseases reputed to be linked statistically with smoking. There appears to be no course available for answering the questions other than by intensive study of the etiology of each such disease. While epidemiology can make some further contributions in ways which will be described, it seems certain that much if not most of the hope for solutions must lie in experimental studies with animal models, carefully balanced against clinical observations on human patients.

Such studies must form a substantial and central core of all medical research in the decades ahead if constitutional diseases are to be deferred or delayed to later age levels. Full solution of the tobacco and health problem will come about as an integral part of better understanding of their etiology.

A positive answer to the fourth question above, in the case of any particular disease, would, of course, remove cigarette smoking from consideration as a possible factor in etiology. A partially positive answer would correspondingly diminish the relative significance of any role that such smoking could play in the etiological picture.

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A positive answer to any one of the first three questions might suggest measures helpful to some degree in prevention, postponement or control of the disease. Definite and positive answer to question number one in terms of how and to what extent cigarette smoking played a role, might lead us to some change in tobacco or tobacco smoke that would have protective value. On the other hand, a definite answer to the second or third question would shift the spotlight from the cigarette to the smoker and suggest attention to the modification of his habits or special protective measures against his hereditary predispositions.

Such answers are not yet available in most cases and the questions must therefore be considered as still open and calling for concerted attack.

Each of the four questions stated suggests different lines of research on each of the several constitutional diseases in question, so that the total number of problems for investigation becomes very large. Research planning could be far more efficient and economical if there were some basis for concentrating effort on any one of these questions to the exclusion of the others. While this basis does not now exist for most of the diseases, any type of inquiry that proffers the hope of definitely including or excluding any one of them in the case of any disease associated statistically with cigarette smoking should be given a high priority regardless of cost, in the interest of eventual economy in money, time and effort. Such possibilities will be pointed out later.

Peptic Ulcer and Cigarette Smoking

Peptic ulcer is not a very large contributor to mortality because it is often arrested or cured so that persons with ulcers ultimately die of other diseases. It is, however, responsible for a great deal discomfort and illness. The term "peptic ulcer" really includes two diseases; ulcer of the stomach and

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ulcer of the duodenum. These are generally believed by physicians to differ in their etiology, though they have some common features. In order to consider any possible role of cigarette smoking in causation or aggravation of these diseases, we really should have figures on their relative incidence in cigarette smokers and non-smokers. We need to know what proportions of people develop ulcers of each type among the groups with different smoking behaviors.

However, at least two epidemiological studies have reported that deaths from ulcer, although not very numerous, were from 2.83 to 4 times as numerous among cigarette smokers as in the general population. These studies were interpreted as showing a strong association between cigarette smoking and ulcer mortality.

As mentioned before, the association raises four broad questions:

1. Is cigarette smoking actually a causal factor in peptic ulcer? Does it contribute in some way to its etiology or aggravation, whether weakly, strongly, directly or indirectly?
2. Is cigarette smoking, especially heavy smoking, rather a sign or indicator of the presence of some congenital characteristic that predisposes to the disease?
3. Is cigarette smoking a practice that happens to accompany some pattern of living habits or practices that cause, predispose to or aggravate the disease without itself being involved causally?
4. Is the association fortuitous or a technical artifact?

The physiological aspects of ulcer etiology, though certainly not fully understood, have been elucidated in some part, and alterations in gastric secretion are believed to influence the course of these diseases. Ulcer etiology is presumably much better understood than the etiology of cancer. Hence experiments could be devised to determine whether nicotine or smoking can influence

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these known physiological factors. New studies sponsored by The Council in three centers involved non-smokers, habitual smokers, normal subjects and persons with a history of duodenal ulcer in well-controlled experimental designs. The volume, hydrogen-ion concentration, free acid, peptic concentration and peptic output of gastric secretions, gastric motility, introgastric temperatures, pepsinogen excretion, pepsinogen in plasma, gastric mucins and gastric juice viscosity were all studied extensively before and after cigarette smoking, or compared during periods of abstention or consumption. Some observations were also included on cigar smoking. In none of these tests, did smoking produce any consistent changes in the parameters of gastric secretion attributable to the tobacco use.

This program would appear to have been quite comprehensive insofar as present knowledge of physiological factors involved in peptic ulcer genesis is concerned. It failed completely to suggest any mechanism by which cigarette smoking could contribute to production or aggravation of the disease. Theoretically such a mechanism may still exist, but until some new concept of the physiological factors concerned in ulcer etiology is advanced, it appears difficult to devise additional experiments that might be illuminating.

The first question has thus received no verification or support from extensive studies that would be expected to show pertinence. No practical suggestion for ulcer prevention through modification of tobacco or its smoke has been implied.

The second question tends therefore to attract the spotlight: "Is cigarette smoking, especially heavy smoking, a sign or indicator of the presence of some congenital characteristic that predisposes to the disease?"

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It is widely believed that peptic ulcer is to some considerable extent a "psychosomatic" disease in which a genetically determined predisposition makes certain kinds of persons respond to certain degrees or kinds of stresses by developing ulcer. Presumably any person might develop an ulcer under sufficient stress but according to this concept, the event would occur most often in those with low tolerance limits.

Persons with low stress-tolerance limits might well smoke cigarettes more often or at a higher level than others in the search for relief from frustration. Such a situation would be expected to produce a statistical association between cigarette smoking and ulcer mortality without any contribution by smoking to causation or aggravation of the disease. On the contrary, if smoking is actually effective in reducing stress, it might to that degree actually help those with low stress-tolerance limits to defend themselves against stress effects and thus exercise some preventive effects against ulcer in the hyper-susceptible.

In summary it can be stated that present evidence from these Council studies fails to support the hypothesis that cigarette smoking contributes to the genesis of peptic ulcer, and is better in accord with the concept that genetic characteristics which predispose to ulcer also tend to encourage cigarette smoking. It cannot be said however that the matter is finally or conclusively settled. Among the kinds of studies still needed are the following:

1. Epidemiological studies to explore any possible statistical correlations between cigarette smoking and the incidence of peptic ulcer, with separate consideration of duodenal ulcer and peptic ulcer as separate clinical and etiological entities.
2. Carefully controlled clinical studies of ulcer healing under defined and controlled regimens, especially in respect to food intake, with random division into smoking and non-smoking subgroups for comparison.

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3. Better methods of defining and classifying stresses and of measuring the reactions of subjects to them.

4. Psychological and psycho-pharmacological studies to assess nicotine or smoking further as a "tranquilizer" or reducer of stress effects.

5. Exploration of other psychological, biochemical or physiological characteristics of duodenal and gastric ulcer patients with a view to finding ways of sharply differentiating between persons of low and high susceptibility.

6. Within a group of highly susceptible persons and preferably without overt ulcer, once these can be identified, observation of the relative incidence of overt disease among randomly selected subgroups who smoke or refrain from smoking.

The first and second of these suggested ulcer studies would appear to be particularly suitable for prosecution by governmental agencies, such for example, as the Veterans Administration. With respect to the third, The Council has heretofore found no promising approaches and awaits the proposal of methods that might be applicable.

The assessment of psycho-pharmacological effects of nicotine and smoking is well under way in several projects sponsored by The Council and other agencies. Significant results are emerging which will be mentioned again.

The Council has sponsored studies which contribute something toward development of a "profile" for identification of the highly ulcer-prone individual. A complete or satisfactory method of identification is however still far from achievement. Because of the difficulties in this area, another tactic should be considered. Identical twins must have identical ulcer predisposition to the extent that this is genetically determined. Hence identification of the hyper-susceptible might be dispensed with if a sufficient population of identical twins could be located in which one partner had smoked cigarettes at a

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significant rate over a significant period of time while the other partner had not. A comparison of ulcer incidence in the smoking and non-smoking partners should assist in separating the effects of congenital predisposition from any contributory influence of cigarette smoking or other external factor.

This plan is not without difficulties. It has already been shown that identical twins tend to adopt similar smoking practices more often than non-identical twins or siblings whether or not reared together or apart. This observation has been advanced as a cogent argument for the existence of congenital factors that influence the need or desire to smoke. Hence a minimum number of identical twins with desparate cigarette smoking habits is to be expected. Among those pairs in which a disparity in smoking practice is found, it would be necessary to look for environmental differences, such as those producing stress or frustration, that might contribute to the disparity. Nevertheless, with suitable controls such a twin study should be informative.

More important than its application to the ulcer and smoking problem is the fact that analogous twin studies might serve in the study of many other constitutional diseases to separate the effects of congenital factors from those of environmental ones. The total promise of such twin studies is great enough to justify the assembly of a large twin registry in the United States. The scale required for a useful registry is such as to recommend that its assembly be undertaken by a federal agency with extensive resources and access to information on very large populations, such as the Veterans' Administration. The numbers of twins necessary for significant study of any particular constitutional disease would be inversely related to the prevalence of the disease and in some cases would be very large.

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Multifactorial Studies

We have pointed out the complexities that are to be expected in the etiology of the constitutional diseases and the numerous factors both internal and external, genetic and environmental, which must contribute to their development either strongly, weakly, directly or indirectly. The existence of such complexities is well-recognized in the case of cardiovascular diseases and in chronic ailments of the respiratory system. They are coming to be better recognized in the pathogenesis of cancer. They are inescapable in the consideration of length of life. Epidemiologists have been importuned to gather data on a wide variety of such factors in their prospective studies of morbidity and mortality from constitutional diseases of the heart, arteries, lungs and from cancer. Such data have been collected in epidemiological studies of lung cancer.

The pressing problem in the field of epidemiology is now to bring the methods of multivariate analysis to bear in cases where data have been collected on the numerous factors suspected of contributing to development or aggravation of the disease. Such methods of analysis can weight the various factors relatively, in a mathematical sense, as contributors to the result. The degree of mathematical contribution may then suggest experimental or clinical experiments for evaluation or verification.

Serious fallacies in perspective can result, we are advised, from the over-interpretation of one-to-one correlations even though they are mathematically sound.

The classic method of carrying out such multivariate analysis was through multiple regression analysis. This is a laborious technique and is difficult to apply in practice when the number of variables to be weighted is very

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great. Nevertheless, in several recent epidemiological studies of heart disease not sponsored by this Council, multivariate analysis of this type has rather dramatically modified perspective on the combination of factors that can predict heart attacks or freedom from these. Cigarette smoking was not an effective contributor in these analyses when considered in relation to others.

It is urgent that this type of analysis be applied generally to multifactorial studies of constitutional diseases and very especially to the data that have been collected in prospective studies of lung cancer.

With modern computers available, new techniques are being developed for accomplishing the same objectives more quickly. The Council has made a special staff service grant to a computer expert for development of new computer programs for rapid handling large numbers of variables and for applying these methods to the analysis of data from Council projects. The promise of these methods suggests strongly that they should be applied to many of the multivariate studies that have been carried out in the past by governmental agencies or that may be undertaken in the future. The new methods of computer analysis should make practical the collection and handling of much more extensive data relevant to the etiology of the constitutional diseases that presently are the greatest sources of illness and death.

Another use of such computer programs is for studying the tendency of other habits and practices of life to "cluster" about cigarette smoking. It is urgent to collect much more data on the differences that exist between the "style of life" and daily habits of cigarette smokers and non-smokers if progress is to be made in distinguishing between any effects of smoking "per se" and the effects of associated life habits in the causation or aggravation of the several constitutional diseases.

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Cancer of the Lung

In a sense this disease holds a particular spotlight with respect to smoking and health investigations because of the reputed "strength" of its association with smoking in monofactorial epidemiological studies. Nevertheless, all the general comments that have been made about constitutional diseases apply as well to carcinoma of the lung.

Another reason for the special spot-light on this disease is the rate at which it is reputed to have increased in incidence within recent decades. This question merits comment.

Trends in Incidence

How much has lung cancer actually increased in this century? We are being told that it is skyrocketing and approaching epidemic proportions. There is much doubt whether this is true. Indeed, the incidence curves show signs of approaching a plateau.

There is a considerable literature showing that lung cancer was well known during the entire nineteenth century by those pathologists who happened to be interested in making autopsy examinations, though not by physicians generally. But lung cancer was usually recognized only post mortem and was rarely diagnosed clinically. Since autopsies were uncommon, we have no way of knowing the true prevalence of the disease in that era.

There is good qualitative evidence, however, of the progressively increasing ability of clinicians to diagnose the disease during the present century, especially as new diagnostic tools such as radiography, bronchoscopy, exfoliative cell examination, and others were perfected and used more generally. A number of hospitals scattered about the civilized world have published reports

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comparing clinical diagnosis with post-mortem findings. During the early years of the twentieth century, carcinoma of the lung was missed in these series as often as nine times out of ten during diagnosis of the living patient. As time went on, the score improved until at present 80 or 90 per cent of such cases in some series have been correctly diagnosed in living patients. If the diagnostic score was formerly no better than this in the hospitals that have published such reports, it is very likely that it was far less accurate among practitioners generally. The effect of a general increase in awareness of the disease coupled with ability to diagnose it in vivo would be to swell the figures for reported mortality for bronchogenic carcinoma.

It is certain, therefore, that the curves showing reported mortality from this disease through the years are considerably steeper than the "true" curves ought to be. We do not know how much too steep they are, and it is not likely that we ever shall. Opinions differ from the view, at one extreme, that there has not been any real increase at all, to the view that most of the apparent increase is real. The difference between these two views may be the difference between concern and panic. The difference between concern and panic may add up to the difference between enthusiasm for concentrated, assiduous, and thoughtful analytical investigation and demand for immediate and precipitous action, whether or not well grounded, and despite the risk that it may degenerate into ineffectiveness gesturing.

We can all agree that the existence of any lung carcinoma at all is sufficient reason for concern and for concentrated hard work.

Primary vs. Secondary Cancers in the Lung

It is well-known that the lung is a favorite locus for metastatic tumors from other primary sites, so that a large number of cancers occurring in the lung do not originate there. Substantial series of autopsy studies have shown that as

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30% of cancers in other organs may metastasize to the lung. It is not to be expected that the complex of etiological factors, particularly environmental agents, giving rise to cancers in these other organs will be the same as those generating primary cancers of the lung. Hence figures for incidence of lung carcinoma must be carefully confined to those cases that are primary in the organ if they are to be significant for ~~epidemiological~~ studies relevant to epidemiology.

Pathologists have produced ample evidence that known metastatic lung tumors can often so closely simulate primary cancers as to be indistinguishable by pathological criteria and therefore identiable as secondary only by location and examination of the primary lesion. Such exhaustive and painstaking autopsy examination of lung cancer decedents is rarely undertaken, so that many authorities consider the true incidence of primary lung carcinoma to be unknown with any degree of precision, either currently or for past decades. This situation greatly obscures the true trends of incidence. A recent exhaustive restudy of accumulated cases in an outstanding medical center suggested an error in distinction between primary and secondary lung cancers at about 18%. If the error was of this order of magnitude at an outstanding center, it was probably much larger in most others. Every effort of the federal agencies to explore this situation and develop any possible measures that will furnish more reliable figures for the incidence of primary carcinoma of the lung is to be urged.

Classification of Lung Tumors

There has been much debate in recent years about the classification of primary lung tumors by cell type, and many hypotheses concerning the differing influences contributory to the pathogenesis of each type. It was held by one school of thought that the squamous cell type was that most likely incited by external agents such as inhaled carcinogenic substances. This type was reported to occur more commonly in males than in females and to be that which was showing the largest increase.

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Recently the more exacting examination of such tumors has confirmed the suspicion that most of them contain a variety of cell types within the same tumor so that classification must depend upon sampling procedures and predominating cell type on a relative basis. Prosecution of this kind of classification procedure now implies that the major increase may have occurred in types of lung cancer that were previously considered unlikely to have been incited by inhaled carcinogens while those that were attributed to the effects of such external agents have not in fact increased. The extension of such exacting histopathological studies of lung tumors is certainly indicated in the hope for clarification of a picture that is considerably confused at present.

Still more recently, beginnings have been made in the study of growth and proliferation of excised human lung cancer cells in culture media. The profound differences in behavior of such cells in a single medium suggests the existence of profound biochemical differences and capacities for proliferation that are not revealed by histopathological examination of dead, fixed and stained tissues. Such behavioral differences in lung cancer cells which would have been considered by the older to be of a single type suggests that there may actually be many more types than heretofore recognized and raises the question whether etiological factors responsible for their genesis may not vary over a wide range.

Animal Studies of Lung Cancer

There are several ways in which animal studies may contribute to the investigation of lung cancer. Inbred strains of mice are available, for example, which possess genetic predispositions to develop certain kinds of lung tumors at a predictable age and at reproducible levels. In such strains the effects of systematic and unitary changes in the external or internal environment, under

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controlled conditions, can be measured. While species differences are sometimes great in the field of carcinogenesis, the discovery of significant effects exerted by external or internal factors on the time or level of lung cancer development in animals will justify clinical evaluation to determine whether similar factors are operable among human subjects.

Suitable animal studies may also be useful for studying the influences of internal or external environmental factors on the cell type (histopathology) of lung lesions that develop under various conditions. Methods have been reported by several investigators whereby rodents may be induced to develop lung tumors more similar in their cellular characteristics to the prevalent human types than those generally found as spontaneous lung tumors in these animals. These methods may provide models for screening the effects of imposed internal and external factors on the time and level of incidence. The use of such models will be referred to again.

Skin Painting with Cigarette Smoke Condensates

When the statistical association between cigarette smoking and lung cancer was first reported, a good deal of rather feverish activity was begun. A number of biologists undertook to paint the skins of mice and other animals with condensates of cigarette smoke prepared by a variety of methods. Many of these methods were crude and poorly controlled, reflecting a lack of appreciation by the experimenters of the degree to which the composition of the condensates could be influenced by the conditions under which the cigarettes were burned and the smoke condensed and stored. As might have been expected, results varied. (Such condensates have come, erroneously, to be called "tars") With the improvement of mechanical smoking techniques, the results of mouse-skin painting

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experiments have become somewhat more consistent.

While long-term painting skin painting of sensitive mouse strains with high concentrations of such condensates has produced papillomas, some fraction of which become mildly malignant toward the end of the life-span, The Council scientists have consistently questioned the relevance of such observations to the problem of human lung cancer. Certainly no simple or direct extrapolation can be made. This skepticism has been based first of all on the great differences in susceptibility to carcinogens between rodents and primates. Extreme differences have long been recognized and recent new observations in tissue cultures have reinforced this view. Human skin has been subjected to repeated exposure to tobacco smoke and condensates in millions of subjects for very long periods of time, yet there is no record of a human skin cancer attributed to such exposure. Medicinal salves used without harm by humans for over a century are quite active in producing skin cancers in mice.

The skin with its protective coating of fatty material differs greatly from the mucus-coated tissues of the respiratory system and would be expected to show radically different responses to contact agents. Such differences have recently been demonstrated in mice by experiments showing that the mucus membranes of their oral cavities are much more resistant to benzpyrene than their skins when both tissues are treated under parallel conditions with identical doses of this mouse carcinogen. Moreover, healthy, intact, rodents have failed to develop pulmonary tumors when made to inhale pure fumes of methylcholanthrene or benzpyrene, although these substances are potent mouse-skin carcinogens.

It must be emphasized, moreover, that condensates of cigarette smoke "tars" are not equivalent to whole fresh smoke in either physical or chemical properties. Chemical and physical alterations occur, some rapidly, in

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smoke following its formation near the burning zone and these continue in the condensate after collection. Not only do such condensates lack all of the gas phase ingredients of smoke but also some of its normal vapor constituents, the latter depending upon the conditions of condensation and storage. Short-lived components of fresh smoke may not survive condensation and storage, while the physical state of the smoke aerosol is obviously quite different from that of any condensate of any age, however prepared or stored.

The situation encountered in the mouse-skin painting experiments may be summarized by stating that it employs the wrong material in the wrong form and the wrong concentration upon the wrong tissue of the wrong animal for any direct elucidation of the human lung cancer problem.

Our doubts of the relevance of this method is reinforced by the observation in a Council-sponsored study that cigar, pipe and cigarette smoke condensates all show a comparable albeit feeble activity on the skins of experimental inbred mouse strains, whereas the statistical incidence of lung cancer among pipe or cigars smokers is reported to be scarcely greater, even though they say that they inhale the smoke, than among non-smokers.

It may be that the mouse skin painting method can serve as a crude tool to guide fractionations of condensate to locate and perhaps identify some of the substances or classes responsible for the mouse skin activity. Removal or reduction of such agents, if undertaken in any quarter, could presumably do no harm and may be regarded by some as an improvement by presumption. We feel no confidence whatever, however, that such developments could be regarded as having identified a hazard to humans or that its removal produced either a "safe" or "safer" cigarette.

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Smoke Condensates in the Lung

Both Council-sponsored investigators and a number of others have introduced condensates of cigarette smoke intratrachcally into the lungs of several animal species in various kinds of solutions, suspensions or emulsions. While these experiments do not resemble very closely any situation normally encountered by humans, they are of scientific interest in that they have not produced cancers of the lung. The negative results of these experiments further confirm the differences in susceptibility between the skin and lung tissues, and are also interesting because some of the components of smoke, including any traces of polynuclear hydrocarbons, are greatly concentrated in the condensates so that the dosages of these were much higher than by any normal inhalation of whole smoke.

On the other hand, carcinogenic polynuclear hydrocarbons such as methylcholanthrene and benzpyrene have produced cancers of various types when introduced into the lungs of hamsters or ducks in some kinds of solutions or emulsions while failing to do so when introduced in other media.

Smoke Condensates Introduced Intravenously

It has been shown that when multiple lung infarcts (scars) are produced in rats by intravenous injection of a fluorinated hydrocarbon, the simultaneous injection of methylcholanthrene (a carcinogenic hydrocarbon) will produce invasive lung carcinomas. The carcinogenic chemical when injected alone into an unscarred lung under the same conditions, did not produce any cancers. When cigarette smoke condensates were injected similarly into the veins of lung scarred rats, no cancers appeared.

Of course the administration of this fluorinated hydrocarbon into the veins is in itself quite unphysiological in the sense that probably no human has

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ever had this experience. Nevertheless, infarctions of the human lung, from one natural cause or another, are common. There is an impressive medical literature reporting human lung cancers that developed in infarcted areas of the lung and around old tubercular scars.

Another animal model has been used in a similar fashion. Certain strains of mice have the genetically determined characteristic of developing a certain type of lung tumor of low malignancy or power to invade. These tumors are ordinarily multiple in nature and are so separate and distinct that the number of them in a lung can be counted easily under low power magnification.

It was shown some years ago that when a carcinogenic hydrocarbon such as benzpyrene is injected into the bloodstream of such mice, the number of nodules developed will be larger in exact proportion to the size of the benzpyrene doses given. When this kind of experiment was repeated using cigarette smoke condensate for intravenous injection instead of benzpyrene, the numbers of tumor nodules did not increase. Indeed, they were somewhat decreased.

Such experiments suggest further study of the role of lung infarction as a contributor to human lung cancer predisposition but do not support the hypothesis that cigarette smoke plays any role in the process. Of course, since the experiments cited used condensates, they are subject to the criticisms and limitations that have already been detailed as pertaining to such preparations.

Whole Smoke Inhalation

Some of the very cogent objections to mouse-skin painting with cigarette smoke condensates as a method for attempting to elucidate the reputed hazards of cigarette smoking to the human lung, might, it would seem, be obviated by suitably designed experiments involving the inhalation of fresh whole smoke by experimental animals. Hopefully, this type of investigation might, under properly controlled

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Source: https://www.industrydocuments.ucsf.edu/tobacco/

 Expand: allow for extrapolation only mechanisms which can then be applied to humans

conditions, deliver the "right material", in the "right concentration" and the "right form" to the "right tissue", if not to the "right animal". By a comparison of species, common effects might be regarded as having general import and might suggest methods of indirect evaluation in the human. While such inhalation experiments are far more difficult technically than skin studies, it is difficult to conceive of any adequate alternative.

Apparently many investigators adopted such a view, for following publication of the statistical reports of an association between lung cancer and cigarette smoking, a number of them undertook studies of this kind. In many laboratories, mice, rats, hamsters, hens, rabbits and dogs were induced to inhale cigarette smoke repeatedly over long periods by means of a variety of mechanical devices. No doubt it was expected that these animals would develop cancers of the lung. Then, it was supposed, the work of fractionating smoke to identify and remove the responsible agents could be carried out. ~~The~~ One obstacle to this plan was that the smoked animals did not develop lung cancers. Indeed the studies added up to an impressive failure. Most of this work was never published in any detail and the extent of the effort is little known even today.

The Council has been sponsoring such studies of whole smoke inhalation by experimental animals since the earliest days of its program. Ten years of persistent work by several independent investigators have, like others, so far failed to demonstrate the development of epidermoid or squamous lung tumors in a variety of animal species as a sequel of such exposure. Inflammatory reactions were sometimes observed, rather erratically and especially where signs of concomitant virus infections were present, as well as other kinds of abnormalities. Many of the untreated controls also showed inflammatory changes.

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The difficulties of inhalation studies have been emphasized before. In retrospect, much of the methodology employed in the earlier work now appears quite crude and inadequate. One major limitation was the lack of any quantitative objective measure of the actual exposure of lung surfaces to smoke, especially to the particulate phase, in either animals or humans. This lack has prevented development of adequate information on dose-response relationships.

Assessment of lung exposure to smoke.

In the case of human epidemiological studies, dependence has generally been placed on data derived from questionnaires, both as to the daily level and kind of smoking and as to subjective impressions of the extent of inhalation of smoke. A recent Council-supported study, not yet published, has shown the very poor reliability of such recall data by comparing the results of several successive interviews with the same subjects at intervals. A separate Council-sponsored study has suggested a substantial role of psychological attitudes in modifying replies to questions about smoke inhalation practices.

These findings further emphasize the need for an objective biochemical method of estimating smoke exposure of the lungs. Conferences on methodology have been held, as described in our Annual Reports, and several exploratory studies have been set up.

Some progress in methodology has been made in the case of human subjects, who if they inhale at all, quite uniformly draw smoke from the oral cavity with admixture of ten to forty volumes of air taken in through the nasal passages. Since human subjects can respond to spoken instructions, the blood levels of carboxyhemoglobin can be related to specific numbers of inhaled or uninhaled puffs, taken at determined intervals. This may serve as a measure of the degree of contact of alveolar surfaces with the gas phase of smoke. If the usual manner of human smoking maintains a relatively fixed ratio between particulate matter

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and gas phase components of the smoke until they reach the alveoli, the exposure of lung surfaces to particulate matter could also be estimated as a first approximation, from blood carboxyhemoglobin levels.

It still remains, however, to apply this and other objective analytical methods that have been under development to a substantial population of human smokers to assess the variation in actual lung exposure to particulates, as a check against questionnaire information. The comparative lung exposures among typical cigarette smokers on the one hand and the smokers of pipes and cigars, on the other, still remain to be explored as they may be affected by the various puffing and inhalation practices of individuals within these groups.

With animals, the problem has proven to be more difficult because of their general practice of inhaling smoke through the nasal passages. In rodents, these passages filter some portion of the particulate matter so that the ratio between particulates and gas-phase components of the smoke is modified in passage and the ratio as it actually reaches the lung is unknown. Moreover, the ability of rodents to suspend respiration for considerable periods of time is a complicating factor.

Carboxyhemoglobin levels have been measured in the blood of mice following various smoke inhalation procedures, and the levels have been shown to indicate substantial contact of lung tissue with gas-plus-vapor phase ingredients. The presence of nicotine, an ingredient chiefly of the particulate phase, has also been demonstrated in the lung following such smoke inhalation. These measurements show that smoke has reached the lungs in substantial amounts. Nevertheless, quantitative estimation of the particulate phase exposure from carboxyhemoglobin levels in the blood will not be justified unless the ratio between particulate matter and gas-plus-vapor phase as the smoke impinges on lung surfaces, can be determined by some objective method.

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Source: https://www.industrydocuments.ucsf.edu/docs/

In recent years many improvements in the techniques for exposing animals to whole tobacco smoke inhalation have been made. From experience, certain principles and requirements have become clear:

1. Mechanically generated cigarette smoke must be produced under conditions closely resembling those in human smoking if it is to approximate the physical and chemical properties of the smoke as it is inhaled by humans. This requires intermittent puffing at suitable intervals with regulation of puff volume, duration, frequency, and length of butt left unburned.

2. Cigarette smoke, after generation, changes rapidly with time in certain properties, notably particle size, and short-lived ingredients may disappear. Therefore, mechanically generated smoke must be delivered to the appropriate tissue of the experimental animal within a carefully controlled time period following formation in the burning zone. This can be adjusted by regulation of the distance between the burning zone and the animal tissues, with appropriate control of flow rate and use of a system that avoids appreciable precipitation or trapping of particulates en route.

3. To approximate the conditions of human smoking, the smoke must be diluted with an appropriate volume of air before contact with the bronchi and lungs. Extreme conditions of exposure, as to undiluted smoke, may be justified for certain laboratory experiments but, in such cases, conclusions with respect to normal human experience obviously cannot be based upon such observations.

4. Smoke produced by blowing air through the burning zone toward the butt end is of essentially the same composition as that produced by drawing the puff from the butt end, provided that free burning is allowed between puffs, and that the volume, duration and spacing of puffs is not modified.

5. To better approximate the ratio between particulate matter and gas-plus-vapor components of smoke encountered by human lung surfaces

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in ordinary smoking, experimental animals should be induced to inhale through the mouth rather than through the nose.

6. To maintain the conditions described in 2 and 3 above, animals should be exposed individually rather than in groups.

Subsequent to this conference, new and improved mechanical devices for exposing animals to smoke inhalation under conditions more closely approaching those set forth above, have been developed. They are currently under trial and adjustment.

A solution to the mouth inhalation problem in mice appears to be imminent and some progress in the quantitative measurement of lung exposure to particulates under standardized conditions has been achieved. Smoke inhalation experiments sponsored by The Council in the future should have the advantage of standardized equipment and methodology where this is desirable for purposes of comparability.

Council studies of the effects of inhaling the gas-plus-vapor phase of smoke free from any particulate phase are in progress for comparison with the effects of whole smoke inhalation. Such investigations are being extended to comparisons of smoke inhaled from cigarette tobacco mixtures with those from typical cigars or pipe tobacco mixtures, in order to assess differences of any kind that may be observed in biological activity. Obviously a very large program could and should be devoted to systematic comparisons of any effects attributable to chronic inhalation of whole-smoke or gas phase from tobaccos of various types, treatments and compositions, and blends.

Predisposing Factors in Lung Carcinogenesis

The resistance of healthy intact rodents to inhaled fumes of pure carcinogenic hydrocarbons, such as methylcholanthrene and benzpyrene, has been mentioned. However, introduction of such hydrocarbons under conditions that

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insure persistence of contact have sometimes been followed by appearance of cancers. Some of these techniques have also involved various degrees of tissue damage or trauma. These experimental findings have given rise to speculations concerning the roles that may be played more generally in lung cancer genesis by factors that influence the efficiency of the normal lung cleansing mechanisms or by lung damage followed by regenerative activity. Such speculations have been extended to consideration of the lung cancer problem in man.

Beware! δ

The existence of predisposing factors to human lung carcinoma is suggested by many epidemiological observations of the human situation. First of all, it is notable that only a minority of persons experiencing comparable exposures to various environmental agents develop cancer of the lung. Sex differences in incidence of the disease suggest a role by hormonal secretions in predisposition. Other endocrine deficiencies or excesses are suggested by studies of lung cancer patients at autopsy. Chronic or repetitive lung infections, persistent occult viruses, damage to the liver, changes in the efficiency of the reticulo-endothelial system, nutritional status, alterations in mucus composition, allergic reactions, and innumerable other factors including even psychological characteristics, have been proposed as predisposing to cancer of the lung.

The investigation of factors predisposing to carcinoma of the lung has thus become an important part of The Council's program and is commended to other sponsors of research. In animal experiments, the effects of mechanical lung trauma and of virus infections are already under study in combination with inhalation of smoke or other agents. In humans, a new investigation of hormonal factors in pulmonary carcinoma has been initiated, which will combine in vivo biochemical observations with post mortem examination of endocrine gland tissues for hypertrophy, atrophy or other changes.

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Animal Models for Lung Carcinogenesis Studies

A truly adequate experimental approach to the broad problem of predisposing factors, however, would appear to require selection of animal models suitable for use in systematic, step-by-step, appraisal of numerous intrinsic and extrinsic factors that may increase or decrease susceptibility.

A satisfactory animal model should provide means of producing a histologically appropriate pulmonary tumor at a numerically substantial and reproducible level, preferably in several different strains and species. A fixed and replicable system of production that yielded tumors at a suitable level in a predictable interval of time, should allow latitude for appraisal of the augmenting or diminishing effects of superimposed single-factor modifications.

Once adopted, such a test system should, of course, be maintained without basic change throughout a long series of screening tests in order to maintain comparability. These facts make selection of the screening system a rather exacting choice. Several possible systems are presently under evaluation or trial. Broad attention to this approach is recommended.

Hints and leads deriving from the use of such animal models in systematic testing must then be employed to suggest observations that can appropriately be applied to the human situation on a clinical basis. In turn, such observations might suggest additional questions that can be explored with animal models.

Lung Clearance Phenomena

Among the factors that influence the rates of clearance of foreign matter from the respiratory tree is the activity of the cilia which propel the mucus blanket with its normal burden of inhaled debris out of the lung. The Council is participating through grants for the basic study of this clearance phenomenon and the factors that increase or decrease its efficiency.

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In such studies investigators have employed a variety of animal preparations, including excised frog oesophagus, clams, etc. While these studies have been scientifically informative, they need to be supplemented by further observations conducted under more physiological conditions in intact mammals.

One hypothesis suggests that depression of the rate of mucus flow may allow inhaled agents from any source to remain longer in contact with lung tissues and therefore increase their opportunity for action. This hypothesis is still untested as a possible factor in carcinogenesis. A direct test might be possible with an animal model of the kind previously mentioned. If such a model system, under basic conditions, could produce a histologically appriate lung tumor at a reproducible level, the effect of influences that depress or stimulate ciliary activity and mucus flow might be tested in long-term experiments with whole animals. Such studies would also require the use of improved inhalation and monitoring techniques if results were to be interpretable in terms of dose and response. Progress in developing such techniques may render possible a better evaluation of the role of mucus flow as a defense against the action of inhaled agents.

As mentioned in Council reports (1963-64), the mucus flow is only one agency involved in the clearance of extraneous matter from the lung. Several investigators in this field assign only about 15% of the total clearance activity to the cilia-mucus system, ascribing a far larger relative role to the macrophages. A Council-sponsored study which measured overall rates of clearance of radioactive dusts from the lungs of intact rabbits has reported that inhalation of cigarette smoke had no measurable effect on total clearance speed. This result has been independently confirmed by a similar study conducted under other auspices.

The implication of these studies seems to be that if clearance of such tagged dusts by mucus flow was depressed by smoke inhalation, some other

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mechanism such as the activity of the macrophages must have been accelerated. Neither study, however, included objective measurement of smoke exposure. Repetitions with more refined techniques may be indicated.

Meanwhile, however, The Council has undertaken to sponsor a direct study of the effects of tobacco smoke on the macrophages, including both possible effects on their mobilization and on the activity of some of their enzymes.

The Investigation of Pathological Changes in the Lung

The improvement of techniques for regulating and quantitating aerosol exposures to the lungs of experimental animals will further emphasize the need for proper interpretation of such histopathological changes as may be associated with these exposures. The general failure of cigarette smoke exposures in animals to produce lung tumors imposes the problem of drawing correct inferences from the presence of any such tissue alterations as may occur. [Moreover, if dose-response relationships are to be deduced, some kind of semi-quantitative method of estimating degrees of change must be developed and employed.]

~~These~~ This problems appears to involve both semantic and conceptual differences among pathologists. We find on the one hand, the concept that hyperplasia, metaplasia, atypical metaplasia and "carcinoma-in-situ" are to be regarded as sequential changes in a progression between normal cells and carcinoma. On the other hand, there is a concept that the change from normality to malignancy in a cell occurs suddenly and invisibly in any given cell without intermediate stages that are histologically recognizable. According to this concept, the hyperplasias, metaplasias and atypias that are very widely prevalent in the lungs of most adult and many young human patients, are to be regarded as "normal" responses to challenges of many kinds. Some regard such deviant cells, however, as a milieu in which occurrence of the subtle "malignant transformation" may be statistically

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more probable. It has been suggested that such transformations may be occurring constantly in all animals, but become overt cancers only when the numbers of transformed cells become so great as to overcome the immunity system or when the latter is depressed by some mechanism.

Various observations have been produced that bear upon these questions without settling them conclusively. For example, the descriptive study of human lung pathology inaugurated by this Council and extended under other auspices, has shown that metaplasias were not more prevalent in the lungs of pulmonary carcinoma patients than in subjects without lung cancer. If metaplasia were a stage in cancer development, one would expect a different picture.

Council-sponsored studies of possible synergistic effects between influenza infections in mice and the inhalation of cigarette smoke have not resulted in epidermoid carcinomas of the lung, though evidences of synergism in proliferative effects were seen. These observations stand despite repetitive experiments with progressively improved techniques. There is no present evidence that cigarette smoke can furnish the secondary challenge which has been suggested as conceivably capable of transforming proliferating lung epithelium into squamous cell carcinoma.

An obvious need exists for the extension of such experiments. More definitive information might be produced by studies in which epithelial proliferation in the lung was first stimulated by a unitary factor such as a virus infection or a non-specific irritant, followed by quantitated treatment with known individual carcinogens (rather than complex and variable mixtures) introduced at measured levels into the respiratory tree.

Meanwhile there has been a resurgence of interest in viruses as possible sole agents in carcinogenesis. In a Council-sponsored study, an influenza virus was cultivated in a mouse tissue culture and modified cells then transplanted

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Source: https://www.industrydocuments.ucsf.edu/docs/kjvh0000

back into host animals. Tumors appeared. This observation has emphasized the necessity of ruling out contamination by other viruses, especially polyoma, that might have played a role in this tumor genesis. Such possible contaminants are being carefully checked by tagged antibody experiments.

The [illegible] of viruses in lung cancer genesis is a field calling for concerted research and much [illegible] of the kind is under way [illegible]

Tissue Culture Studies

Tissue culture studies are also being employed in efforts at an elucidation of the questions posed by observation of pathological changes in the lung. One possible method of detecting "malignant transformation" in cultured cells is to plant them back into host animals and observe directly their potential for growth, invasion and metastasis. A study of this kind has been inaugurated. Its object is to determine whether histological changes induced by various treatments of lung tissue in culture and analogous in appearance to those found in human lungs at autopsy are actually "precancerous" -- that is, capable of progression to cancer without further modification by external factors. The development of culture techniques suitable for such a purpose is complicated by the experience of Earle and Sanford who reported that some untreated cell cultures after in vitro cultivation for several generations, grew into malignant tumors following retransplant into animals. A Council grant is providing for repetition of this work with special attention to the exclusion of virus contaminations that might have produced such a result, as the cited authors postulated might have occurred.

Another new study sponsored by The Council will observe specifically the changes induced in in vitro cultures of human tissues by various virus infections.

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SMOKING AND THE CARDIOVASCULAR DISEASES

Diseases of the heart and arteries are the leading cause of death at the present time. The most important of these are the so-called ischemic diseases, that is, those in which an obstacle to proper flow of the blood (occlusion) results in a lack of oxygen to some organ or segment thereof. The manifestations of such occlusion may be gradual and chronic as in "angina pectoris" or sudden and acute as in "heart attacks" or strokes.

What area?

In this area also, epidemiologists have reported a statistical association between cigarette smoking and the incidence of or mortality from diseases of this class. Here also, all the general kinds of questions that are raised by any such association, as set forth above, are quite pertinent. Again the smoking of cigars and pipes seems not to be implicated in the associations, but only cigarettes. Since deaths from constitutional diseases of the heart and arteries are very much more frequent than deaths from ulcer or the various forms of cancer, especially lung cancer, any factor that actually caused even a small increase in deaths from these diseases would be responsible for much more "extra mortality" than one which caused a large relative increase in some less common disease.

It is being stated by many persons that cigarette smoking is such a factor and that by "causing" a relatively small increase in death rates, it is responsible for a very large number of extra deaths. In actual fact, this has not been established by any means, and recent discoveries make any such conclusion very improbable.

The ischemic diseases of the circulatory system are another group which quite generally understood to be "caused" by a large number of contributory

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factors. A hereditary predisposition is widely recognized as playing some part, including body build, emotional makeup, personality and ability to tolerate stress. Environmental factors such as "stress", diet, physical activity, use of common drugs, coffee, tea and alcohol, hours of sleep, have been implicated by various investigators. "Mixed factors" that may be partly hereditary and partly environmental include high prevailing blood pressure, obesity, high serum levels of cholesterol and other lipid materials, rapid heart rate and others.

Several epidemiologists have conducted multifactorial prospective studies in the hope of identifying the factors, both external and internal, that will best predict the probability of getting a heart attack or of avoiding one. In such work as this, the methods of multifactorial analysis that have been mentioned are much needed, and the newer and faster computer techniques should help expand and expedite researches of this character. In some cases multiple regression analysis has already been applied in order to assess the various individual factors as to their contribution to the "predictive power" of the whole combination. This predictive power is a purely mathematical concept and does not of itself demonstrate any causal involvement of the particular factor in question. On the other hand, if a particular factor does not contribute mathematically to the power of the constellation of factors to predict the disease or to select out the candidates for early attack, that factor is an unlikely candidate for suspicion as one involved in causation.

In several recent studies of this character, in which multiple regression analysis or its equivalent was used, the factor of cigarette smoking was found to contribute little or nothing to the predictive power of the constellations of factors that were able to distinguish persons susceptible to heart disease from those who were not. This was the case even when simple one-to-one correlations of smoking with mortality from the disease were found.

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Source: http://www.industrydocuments.ucsf.edu/tobacco/

In one study, the investigators attempted to separate a large sample of middle-aged men, none of whom had so far sustained any heart attacks, into those more likely to suffer attacks and those least likely to do so, using a battery of tests, measurements and observations that they had come to feel would have "predictive power." After several years it was found that their predicted susceptible group had actually experienced many more attacks than the group they had picked out as resistant. Then they undertook to revise their battery of predictive observations in the light of actual experience in the hope of getting a more accurate separation the next time. They report that cigarette smoking as a factor was not useful in separating the candidates for heart troubles from those who would be immune.

Other long term studies of similar character must still wait a good many years before the health experience of the subjects will allow any conclusions to be drawn.

My view is that still further well-planned prospective epidemiological studies of heart disease incidence can produce useful clues for laboratory and clinical study of etiological factors if such studies include many possible contributory factors and these are weighted as to their relative predictive power by modern methods of multivariate analysis. Much of the existing data of this kind need reanalysis by such methods.

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Cigarette Smoking and Atherosclerosis

There is a broad consensus to the effect that the process of atherosclerosis predisposes to ischemic diseases of the heart and blood vessels. This process involves the gradually thickening of the arterial walls by lipid infiltration, plaque formation, calcification etc. It occurs quite generally

Source: https://www.industrydocuments.ucsf.edu/tobacco/

in humans, beginning at an early age and progressing gradually at rates that vary widely from person to person. As the walls thicken, the flow of blood is impeded and may become insufficient to furnish adequate oxygen to the tissues supplied by the vessel. The insufficiency will first show up when oxygen demand is increased as by exercise, emotion or other influences. As the process continues, oxygen supply may become insufficient even in a state of rest. Sclerosed vessels also tend to lose their elasticity and may become unable to dilate under influences that would normally enable them to expand and deliver more blood under stress. A complete blocking of a vessel by a clot (thrombus), a particle of debris (embolism) or some other mechanism (spasm?) is an occlusion. Depending upon its location, an occlusion may produce a "heart attack", a stroke or other acute manifestation.

The acute pain called "angina pectoris" is a referred pain caused by lack of oxygen in the heart muscle. As a relatively chronic condition, occurring most often when exercise, emotion or other stress creates an oxygen demand that is not met, angina is generally attributed to thickening of the coronary artery walls, short of complete occlusion. This, however, is somewhat controversial.

Major prospective epidemiological studies have reported that angina occurs no more frequently among cigarette smokers than among non-smokers. This lack of association has been interpreted as evidence that chronic smoking does not contribute to the progression of the atherosclerotic process,

This evidence was supported further by several post mortem studies in which the degree of thickening in the arteries was carefully measured and was found to show no significant difference in smokers and non-smokers of cigarettes.

Recently a more extensive post mortem study of this nature has been reported in a preliminary manner. In this case some degree of positive correlation

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was found between the atherosclerotic thickening and cigarette smoking history (as determined by interview with near kin of the deceased). However, since many other habits and practices of life tend to cluster differently around the practices of cigarette smoking or non-smoking, it cannot be concluded that the smoking, per se, was responsible for the difference.

Nicotine and Atherosclerosis

Atherosclerosis is reported to be quite rare in animals in the wild state, though it occurs in several types of primates in captivity, especially on special diets. Dogs, rabbits and hens develop a kind of atherosclerosis, not wholly like that common in men, under special regimes of treatment including diets containing a great deal of cholesterol. Rodents have not been found suitable for atherosclerosis studies. Systematic whole tobacco smoke inhalation studies are difficult enough to conduct with rodents, as has been described, and methods have not yet been developed suitable for long term, chronic smoking of larger animals.

However, since nicotine is pharmacologically the most active agent found in tobacco smoke, attempts have been made to determine whether chronic dosage of hens or rabbits fed an atherogenic high-fat and cholesterol diet would speed up the process of atherosclerosis in these animals as compared to those on the special diet only. No clear or convincing effect of the nicotine addition was found. As an experimental model, this system has deficiencies. If this kind of approach to the problem is to be really meaningful, it should involve an animal that will develop atherosclerotic lesions in a reproducible manner, of a nature quite analogous to those in man, and on a dietary regime as close as possible to that used by man and devoid of extreme abnormalities. The possible effects of nicotine chronically administered should be compared with the effects of chronic whole cigarette smoke inhalation under the conditions described and

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Source: https://www.industrydocuments.ucsf.edu/docs/kjwj0000

defined elsewhere in this paper, if techniques can be developed for making this possible with larger animals, especially primates.

Atherosclerosis and Cardiovascular Disease in Pipe and Cigar Smokers

In any consideration of nicotine in relation to atherosclerosis, the anomalies presented by pipe and cigar smoking must be resolved. The epidemiological studies have shown that pipe and cigar smokers experience virtually no more heart disease than non-smokers." A number of studies have shown that pipe and cigar smoke contain more nicotine than the smoke of most cigarettes and that a greater proportion of the alkaloid is in a free state that is readily absorbed even through the mucus membranes of the mouth. Moreover, a substantial proportion of pipe and cigar smokers report that they inhale. If, on average, pipe and cigar smokers receive about the same nicotine dosages as cigarette smokers, and yet differ markedly in their experience of cardiovascular disease, the reported increased incidence of such disease in cigarette smokers cannot easily be attributed to nicotine. It would be necessary to assume that the same total dosage received in a different pattern could produce different effects. This subject is being studied and obviously needs to be settled.

The need for physiological methods of measuring actual nicotine absorption, as by blood or urine analysis, has been mentioned in another connection. Methods for accomplishing this need to be perfected and then applied to large numbers of cigarette, pipe, and cigar smokers under the normal conditions of their lives.

It has been suggested, of course, that the difference in disease experience of pipe and cigar smokers on the one hand and of cigarette smokers on the other, will ultimately be found due to constitutional differences, which are

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reflected in their smoking preferences. There is already evidence that the distribution of body build types is different among cigar and pipe smokers than among cigarette users. A clarification of the nicotine question would help determine how much effort should be devoted to solving questions of constitutional influence. The "pattern of life" studies recommended for elucidating the different clustering of habits, activities and behaviors with cigarette smoking as compared to non-smoking should also be extended to pipe and cigar smokers for the same reasons. Since smoking and the use of alcohol, for example, are associated, it is expecially important to make comparisons of the constitutional disease incidence and mortality rates of non-smoking drinkers and non-drinking smokers, smoking drinkers, and non-smoking non-drinkers.

Diet and Atherosclerosis

This is a controversial topic that has produced a voluminous literature. There appears to be quite general agreement that faulty metabolism of fatty substances is somehow involved in the atherosclerosis that is believed to underlie much cardiovascular disease. However, until a more definite pattern emerges which can successfully integrate such factors as the kinds and amounts of fats consumed, the inborn metabolic differences of individuals, physical activity in relation to the amounts and kinds of food consumed, and others, the exact role of fat metabolism will not be clear. Further and more precise studies to determine the extent to which cigarette smokers and non-smokers differ in their selection of foods and metabolic handling of these might help clarify these problems.

A recent large scale study of surviving heart attack victims showed a much lower incidence of new attacks among those who were kept on a "prudent" low-fat, low cholesterol diet than among those who continued on a "normal" American type diet, although both groups continued in their usual smoking practices.

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Physical Activity and Atherosclerosis

A number of studies of workmen whose regular employment involves differing degrees of physical activity have been consistent in showing a lower rate of heart attacks or of cardiovascular abnormalities among physically active persons than among sedentary ones. This raises the question whether cigarette smokers tend to exercise more or less in general than non-smokers or whether sedentary persons tend to smoke more.

Psychological Stress and Cardiovascular Diseases

One group of investigators have reported that a certain psychological type of person characterized by a low tolerance to certain kinds of emotional irritation are more likely to experience heart attacks than the type which shows little low response to such irritations. Somewhat as in the case of ulcer, this raises the question whether the type which responds strongly to these stresses are more likely to smoke than those who are unaffected. A further question is whether the smoking actually helps to relieve the emotional tensions generated in these stress-susceptible persons.

Another extensive study has shown that professional people in specialties whose work imposes severe strain have more heart attacks than colleagues in the same profession but engaged in specialties that impose less stress. For example, surgeons have more heart attacks than dermatologists. Those in the stressful specialties also tend to smoke more, but this was considered by the investigator to be a result of the stress. Those who stopped smoking had fewer heart attacks than those who had never smoked, which was interpreted as showing that the previous smoking could not have built up any cumulative effect such as increased atherosclerosis. If the cessation of smoking involved a process of selection which separated out a group that had minimal need for stress relief, the phenomenon described supports the hypothesis that stress, poorly tolerated, is a contributor to precipitation of heart attacks.

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Indeed, some persons who have died of a sudden "heart attack" show very little sclerosis of the coronary arteries, while others who have never had any heart symptoms ~~have [illegible] of other [illegible]~~ and have died of other ailments may show a ~~[illegible]~~ very marked amount of thickening in the artery walls, ~~with~~ This situation raises puzzling problems about the factors that ~~may~~ precipitate an acute attack ~~where an~~ and the relation of these to the conditions of arteriosclerosis that are regarded ~~underlying condition of arteriosclerosis exists~~ in general as increasing the danger.

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Smoking and Thrombosis

The role that clot or thrombus formation may sometimes play in producing occlusion of a blood vessel has been mentioned. The problem of thrombosis as a factor in ischemic heart disease is complicated by the fact that often no thrombus is found post-mortem in the arteries of those who have died suddenly of a clinically typical "heart attack." INSERT Nevertheless, since thrombus formation certainly plays some role in many ailments of the ciruculation, any effects of smoking or of nicotine on the coagulation or clotting mechanisms need to be studied. It is very difficult to plan meaningful investigations in this area. The study of blood clotting in the test tube has been very complex and many "factors" have been described that are believed by various experts to play a role in the process. However it has to be admitted that all studies in test tubes are highly artificial and may not reflect at all well what actually happens inside the vessels.

While there is an enormous literature touching on the effect of smoking on thrombosis, the behavior of the "platelets", whose adherence to one another is considered to be one of the first stages in thrombus formation, and on various coagulation phenomena in the test-tube, there is little direct information from which definite conclusions can be drawn.

There is certainly need for more precise and more accurate methods for measuring those aspects of blood that are crucial to thrombus formation in flowing blood. The behavior of platelets would appear to be especially important but present methods of study contain gross errors. Tests of the earliest stages of coagulation are held by some to be probably the most important. There is need for very carefully controlled experiments, especially with stringent regulation of diet, to study any changes occurring immediately after smoking, in the blood constituents which are related to thrombogenesis.

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Source: https://www.industrydocuments.ucsf.edu/tobacco/docs/

No study so far, is extensive enough to provide any compelling evidence.

Smoking and Hypertension

Although chronic elevated blood pressure$, especially diastolic pressure, is implicated in several epidemiological studies as one factor increasing the likehood of "heart attacks" there is little evidence that smoking causes hypertension.

The first morning cigarette is reported to bring about a slight elevation of blood pressure which tends to be sustained by subsequent smoking during the day but without further elevation.

A number of studies have reported, however, that the resting blood pressures of habitual smokers who have not smoked recently are generally lower than those of non-smokers. Whether this reflects an increased need or desire to smoke on the part of persons whose blood pressures tend to be relatively low, a dislike of smoking by persons whose pressures tend to be higher, or whether it reflects some kind of an adjustment to chronic smoking is not dear. A resolution of this question might help settle a number of the problems that have been mentioned.

Nicotine and Smoking in Relation to Blood Flow

At one time nicotine as suspected of being a"constrictor substance" which could cause the arteries to contract and reduce the flow of blood. In the case of the arteries that supply the heart and other vital organs, a constrictor might have deleterious effects, especially in the case of arteries already narrowed by atherosclerosis.

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Source: https://www.industrydocuments.ucsf.edu/docs/kjwj0000

New methods of more directly measuring blood flow in the arteries that supply the heart have shown that nicotine, instead of being a constrictor of these arteries, has a dilating action that, in normal subjects, increases the flow of blood through these vital vessels.

However, nicotine also has a kind of stimulant effect that, like mild exercise, tends to increase the heart rate a little and to raise the force of its contractions. This produces a greater output of blood but also increases the need of the heart muscle for oxygen. If the coronary arteries have been rendered stiff and inflexible by atherosclerosis, they may not be able to dilate for accommodation of this increased need for blood.

In these respects, therefore, smoking has much the kind of effects that climbing a staircase will produce. They should not harm any normal person and could be deleterious only to a persons who arteries were so diseased that climbing a stair could be hazardous.

In the extremities, it has been shown clearly that nicotine or smoking may decrease blood flow in the skin of the fingers and toes but increases flow in the skeletal muscles, if these are healthy enough to respond to normal influences.

Pharmacology of Nicotine

Many references to nicotine pharmacology have been made in this paper under other headings.

There is a vast literature on the subject, which dates back into the early nineteenth century. Nicotine has a multiplicity of actions, which are highly dose-dependent. Overall responses may therefore appear paradoxical. The complexity of the responses and their dose dependency probably conduce to the

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expression of individual differences among human subjects, dependent on the relative reactivities of their various systems as determined by genetic factors and modified by life experience.

In low concentrations, nicotine has a stimulating action on certain chemoreceptors which initiate reflexes affecting many parts of the body. The most important of these are the receptors of the carotid and aortic bodies. Somewhat higher concentrations can stimulate both the sympathetic ganglia and the parasympathetic ganglia while still higher concentrations block or paralyze ganglionic transmission. Since sympathetic and parasympathetic nerves in general mediate opposite effects, these dual effects of nicotine can contribute to the appearance of paradoxical responses. The interpretation of the effects of nicotine is further complicated by the fact that it stimulates the release of epinephrine from the adrenal medulla and from other depots. The effects of this hormone on the circulation resemble in many respects those of nicotine itself.

A persistent and very practical problem is to appraise the significance of responses that human subjects may show from such nicotine absorption as occurs within the range of that normally received from ordinary tobacco use. Failure to so appraise the results of animal experiments conducted with higher dose ranges has led to many questionable extrapolations in the past.

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It must be noted ~~also~~ that all the pharmacological effects of nicotine are very transient, because of the rapid metabolism and excretion of this alkaloid, and that no chronic or cumulative effects have been reported.

While it is impossible here to summarize this vast subject adequately, it can be stated that reviews of all the complex but brief pharmacological effects of nicotine on the body do not suggest that the small doses ordinarily received by normal people in the course of ordinary smoking can be a significant health hazard. ~~or contribute to the production of [illegible]~~

Cardiovascular Disease in Twins

A recent and very significant study published in Sweden goes far toward resolving the question whether smoking contributes to the causation of cardiovascular diseases.

We mentioned above the study of identical twins for separating genetic factors predisposing to disease from environmental ones. The twin registry maintained in Sweden permitted location of a significant number of identical twins one of whom had smoked cigarettes over a considerable period, while the other had not.

Rather extensive comparisons of disease and function of the cardiovascular systems of these twins showed no difference between the smoking and non-smoking twins. The incidence of cardiovascular abnormalities was therefore concluded to be determined chiefly by heredity, with no discernable effect of smoking. This study will become the more convincing as time passes and the twins are compared repeatedly in the future as they grow older. One may hope that eventually, post mortem comparisons of the condition of various organs, including the heart and arteries, will be made.

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If a still larger group of twins can be assembled for this kind of study and if the Swedish results are confirmed, the question of any contribution of cigarette smoking to causation or progression of cardiovascular diseases may be settled definitely in the negative.

For this reason, my strongest recommendation is that a twin registry be set up in the United States for a study of this kind as well as for other purposes that have been outlined.

If another and larger twin study settles the question of tobacco use in relation to circulatory diseases, many of the studies heretofore recommended may not be necessary with respect to the tobacco and health question. Many of them will still be needed for the objects of learning how to prevent or defer the onset of cardiovascular ailments.

Oral Cavity Research

The oral cavity is subjected to direct contact with smoke derived from pipes, cigars and cigarettes more rapidly and in greater concentrations than the lungs. Despite this, the incidence of cancer of the oral cavity has shown no significant increase in amount, or of incidence at an earlier age, during the decades in which per capita exposure to cigarette smoke has increased greatly. It is important to find the explanation for this fact.

As mentioned previously Council studies have shown that the oral tissues of mice are far more resistant to benzpyrene, a carcinogen, than their skins.

Since human victims of oral cavity cancer very often show liver damage in mice by either poisons or by dietary difficiencies was studied in relation to their susceptibilities to this same carcinogenic substance. It was found that

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such liver damage markedly increases the susceptibility of both skins and oral cavity tissues to cancer formation. Parallel experiments were made with tobacco smoke condensates. While liver-damaged mice developed some skin tumors, tobacco smoke condensates failed to induce cancers inside the oral cavities of mice even in the presence of such liver impairment.

Liver damage is therefore another factor to be considered in relation to cancer predisposition in general. This phenomenon should be included in studies of lung cancer predisposition in any animal system developed according to the recommendations we have made above, and considered in human clinical studies.

Since the oral mucus membranes resemble those of the lung much more closely than they resemble the skin, and since the oral tissues are much more accessible to observation than the lung, a much more intensive study of oral cavity tissue responses to various kinds of challenge needs to be undertaken.

The usefulness of the oral cavity tissues for studies of tobacco smoke effects is not limited to their service as a kind of substitute model for the lung. The saliva and oral tissues also serve as a first line of defense against external agents and have functions worthy of extensive study in their own right.

The Council has undertaken several such studies and we commend a further consideration of oral cavity research to other sponsors.

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Chronic Pulmonary Diseases

Chronic and progressive diseases of the lung, such as bronchitis, asthma and emphysema are attracting increasing attention as causes of disability and death. Clinicians report that such ailments are being seen more frequently and they are appearing more often on death certificates as causes of decease.

Source: https://www.industrydocuments.ucsf.edu/docs/xxxx0000

The increase in chronic and progressive pulmonary diseases has been attributed in part to the now frequent cure of acute lung infections by antibiotics so that more people with damaged or susceptible lungs are alive today than formerly. Also, as has been pointed out, the component of older people in the total population is greater than ever before in history. In this age group, and expecially in males, these diseases are most frequent.

In this area, the statistics are even more confused than in the case of cancer or cardiovascular diseases by problems of diagnosis and nomenclature. The term "emphysema" has anatomical definitions and the pathologist uses the term to describe a condition that can be recognized under the microscope, and classified as to type and estimated in extent. The general practitioner, however, has come to use the term as practically synonymous with a clinical report of difficulty in breathing.

There is abundant testimony that persons diagnosed clinically as having severe "emphysema" often show little or none anatomically, when examined post mortem. Conversely patients who have had little breathing trouble in life may show extensive anatomical emphysema at autopsy.

Hence extravagant statements concerning the extent to which "emphysema" has increased over any given period as a cause of death have limited meaning.

Obviously etiological influences cannot be studied except in terms of well-defined conditions, as has been stated before. Nor can meaningful epidemiological studies be conducted unless field methods for diagnosis and differential identification and naming are reliable and consistent. Many authorities doubt that the definition of chronic bronchitis as cough of a certain duration together with sputum in certain amounts imposes adequate criteria for the classification. There are certainly many different bases for cough, including neurogenic stimuli of minor character that may bear no relation to bronchitis.

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For these reasons we most particularly need clinical studies in depth that can develop criteria for differential clinical diagnosis, follow the origins and course of development of distinguishable conditions, develop more consistent nomenclature and furnish methods suitable for mass studies in the field. Extensive post mortem examinations to correlate anatomical findings with in vivo lung function, symptoms, biochemical, bacteriological, and radiography should certainly be conducted, in the light of clinical course, life habits and experiences, medical treatments, hereditary relations and the like.

Experimental approaches to emphysema through animal models certainly need to be developed further. The long term chronic effects of inhaling gases such as sulfur dioxide and the oxides of nitrogen, with and without damage by viruses and other infections, can hopefully be conducted in such a way as to throw light upon the relation between anatomical and other characteristics of lung lesions so induced and the lesions of emphysema. The studies of chronic cigarette smoke inhalation in animal experiments of the kind already described, may also throw light on the emphysema problem. In such inhalation studies, it is of course, permissible to employ exaggerated dosages in order to determine the kinds of effects that may be found under extreme conditions. But before implications can be drawn from such studies for application to man, sufficient work must be carried out to clarify the dose-response relationships and permit a reasonable estimate of effects under the actual conditions of life.

Since the so-called "lung surfactant" appears to have profound influence on the elastic properties of lung tissue, which properties are abnormal in true emphysema, further study of the origins and properties of this substance are indicated. Effects of short-term or chronic smoking on surfactant may be relevant to the problem, and methods for stimulating its production when deficient might be very valuable clinically.

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Variations in the abundance and properties of mucus, particularly any bacteriostatic functions or ability to serve medium for the proliferation of bacteria, as these properties may be affected by internal and external factors including contact with tobacco smoke, are a field for relevant study.

In many respects the study of chronic pulmonary diseases is still in its infancy and the role of cigarette smoking as a causative or contributory factor is almost wholly undefined on any scientific basis.

Nicotine and the Central Nervous System

In many sections of this discussion there has been a recurring question as to whether certain kinds of people especially need or want to smoke under the conditions of modern life. We have inquired whether some persons may smoke because of a need for relief of tension. This raises the question whether such relief is actually provided by smoking.

In the past, we have been largely dependent upon the subjective statements of smokers as to why they like or need to smoke. Among the recurring reports are such as these: (1) "It gives me pleasure," (2) "It gives me a pick up and helps me get going in the morning," (3) "It helps me relax when I am tense."

Such statements raise the question whether evidence to check their import can be provided by any experimental method. Some answers may perhaps be furnished by psychological investigations and any promising approaches along such lines should be encouraged.

Another approach is through the methods of psycho-pharmacology, a relatively new field of science. Interest in the psycho-pharmacology of nicotine was greatly stimulated when Swedish scientists showed that nicotine concentrates rapidly and directly in the brain after absorption into the body. This raised interest in the direct effects of nicotine on the central nervous system and how these will be reflected in behavior.

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By the study of electric brain waves (electro-encephalograms) it has been shown that both in animals and man, nicotine has a brief stimulatory or "arousal effect" on the brain, especially when it was originally in a state of what might be called repose. This effect soon subsides and somewhat larger doses of nicotine, administered to animals in such a way as to prolong its action, produces a state somewhere between alertness and sleep that lasts longer. When the brain is in the kind of state associated with agitation, nicotine has an effect on brain waves resembling that of some of the tranquillizers.

Thus psychopharmacology is providing some scientific substantiation for the seemingly contradictory subjective testimony of smokers. It may arouse the sleepy and calm the agitated.

Since direct electrical stimulation of certain parts of the brain produces an effect that is "pleasureable," it needs to be determined, if possible, whether nicotine also stimulates the "pleasure center" directly.

Ingenious devices are permitting monkeys to inject themselves with nicotine and other substances at will. They find this pleasureable after getting adjusted to it, and take considerable amounts spontaneously. This technique is now being used to determine how the amounts taken will be affected by such things as changes in light, food, water and other variables. With some drugs, the monkeys will take ever increasing amounts until they kill themselves, but with nicotine this is not the case. No animal has shown any bodily damage after taking as much nicotine as he wanted, over considerable periods. Many possible extensions of this technique can be envisioned. If some method could be devised for placing the animals under controlled stress or frustration, the effect on their spontaneous nicotine intake might elucidate one of the important questions we have raised.

Several studies have also explored the effects of nicotine on the learning process in rats, using various rewards to stimulate the animals to learn

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their way through a maze, press levers in some pattern or avoid an electric shock by jumping to a wooden pole on signal. Several such experiments seem to show that nicotine may stimulate the learning process, more particularly among the animals that are originally relatively slow learners.

Summary.

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